IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No:	10/695,291
Applicant:	Hua Tang *et al*.
Filed:	October 28, 2003
Title:	PROPOFOL WITH CYSTEINE
TC/A.U.:	1612
Examiner:	Carlic K. Huynh
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APPEAL BRIEF UNDER 37 C.F.R. § 41.37

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Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

S I R :

Appellants hereby request consideration and reversal of the Final Rejection dated May 4, 2008 of claims 1-8 and 10-16.

This Brief is presented in the format required by 37 C.F.R. § 41.37, in order to facilitate review by the Board. In compliance with 37 C.F.R. § 41.37(a)(1), this Brief is being filed within the time allowed for response to the action from which the Appeal was taken or within two months from the date of the Notice of Appeal, whichever is later.

The fees for filing a Brief in support of an Appeal under 37 C.F.R. § 41.20(b)(2), together with any extension fee required in connection with the filing of this Brief, are provided herewith.

I. REAL PARTY IN INTEREST

The real Party In Interest in this matter is Transform Pharmaceuticals, Inc., a wholly-owned subsidiary of Johnson & Johnson, by virtue of an assignment recorded on May 13, 2004 at Reel/Frame 015313/0137.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences related to the subject matter of this Appeal.

III. STATUS OF CLAIMS

Claims 1-16 are pending in the application. Claims 1-8 and 10-16 stand rejected. Claim 9 stands withdrawn. Claim 17 was previously cancelled.

IV. STATUS OF AMENDMENTS

No amendments were filed subsequent to the final rejection.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Various formulations of the anesthetic agent 2,6-diisopropylphenol (propofol) comprising cysteine are claimed.

Independent claim 1 recites a pharmaceutical composition comprising propofol and cysteine. The composition is described throughout the specification, for example, on page 4, lines 9-18 (describing propofol), page 4, lines 28-29 and page 8, lines 22-24 (describing cysteine), and page 5, lines 8-11 (describing propofol compositions comprising cysteine).

Independent claim 11 recites a pharmaceutical composition comprising propofol, a water immiscible solvent, a surfactant, and cysteine or a salt thereof. The composition is described throughout the specification, for example, on page 4, lines 9-18 (describing propofol), page 7, lines 3-6 (describing water immiscible solvents), page 4, lines 22-25 and page 6, lines 16-18 (describing surfactants), and page 4, lines 28-29 and page 8, lines 22-24 (describing cysteine).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Applicants appeal the rejection of claims 1-8 and 10-16 under 35 U.S.C. §103(a) as allegedly obvious over U.S. Pat. No. 6,147,122 ('Mirejovsky") in view of

U.S. Pat. No. 7,097,849 ("Mishra") as evidenced by Bulet et al. (1999) Developmental and Comparative Immunology, 23:329-344 ("Bulet").

VII. ARGUMENT

The Claimed Compositions Are Not Obvious Over the Cited Art Because A *Prima Facie* Case For Obviousness Has Not Been Established

The final rejection does not establish *prima facie* obviousness over the art of record. Accordingly, the final rejection of the claims is improper and should be reversed.

The rejection alleges that the primary reference, Mirejovsky, describes propofol compositions, but acknowledges that Mirejovsky does not teach or suggest inclusion of a local anesthetic or cysteine as an antimicrobial agent. The rejection further alleges that Mishra describes propofol compositions comprising a local anesthetic and an antimicrobial agent, at the same time recognizing that Mishra does not expressly teach or suggest using cysteine as the antimicrobial agent. To remedy these omissions, the rejection states that cysteine is known in the art to be an antimicrobial agent and attempts to support this contention with Bulet, which describes insect defensins, cysteine-containing antimicrobial polypeptides.

A. All of the limitations of the claimed invention are not taught or suggested by the cited art.

The cited references, when considered alone or in combination, do not teach or suggest all of the limitations of the claims. More specifically, the record contains no teaching or suggestion that cysteine is an antimicrobial agent or that it could serve as a preservative for propofol. Therefore the references, even if combined according to the rejection, do not teach or suggest the claimed combination of propofol and cysteine.

The primary reference, Mirejovsky, describes propofol compositions that use sulfite salts as bacteriostatic agents. Mishra describes aqueous propofol compositions that may optionally contain, but do not require, antimicrobial

preservative agents. Bulet describes antimicrobial proteins found in insects, including defensins. None of these references describes cysteine as claimed, *i.e.*, free and not as a residue within a larger protein structure. For this reason alone the combination of disclosures advanced in the rejection fails to discharge the Office's *prima facie* burden.

To bridge this gap between the art and the claims, the rejection relies on two unsupported contentions - first, that cysteine is generally known to be an antimicrobial agent, or second, that Bulet teaches that cysteine is an antimicrobial agent. Absolutely no evidence in the record has been offered for the first contention, and the second depends on mischaracterizing and stretching the teachings of Bulet beyond what one of skill reasonably would have understood from the article.

The record contains no evidence that cysteine was known in the art as an antibacterial agent in any environment. Indeed, not one of the references relied upon in the present rejection discusses free cysteine per se. The rejection alleges without citation that cysteine is known to be an antibacterial agent (see, *e.g.*, October 10, 2007 Office Action, page 6, lines 14-15 and February 4, 2008 Office Action, page 6, lines 1-2). Applicants are unaware of any specific knowledge or teaching in the art that cysteine is antibacterial, and the rejection provides no reference or other evidence to support this assertion. Unsupported allegations cannot establish obviousness. See, *KSR Int'l v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007) (citing *In re Kahn*, 441 F.3d 977 (Fed. Cir. 2006) ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")(internal quotation marks omitted).

The rejection reasons that cysteines are antimicrobial from the fact that the defensins described by Bulet have antimicrobial properties and contain cysteines (see, February 4, 2008 Office Action , page 3, lines 11-13). This mischaracterizes and extends teachings of Bulet beyond what reason bears. Bulet describes insect defensins that are antimicrobial polypeptides with shared cysteine-paired domains (see, *e.g.*, page 330, paragraph 2.1 and Figure 1). Bulet never says or suggests

that the antimicrobial properties of the defensins arise directly or even indirectly from the cysteine residues. Paragraph 3 of Bulet (page 332) describes the known biological activity and mode of action of insect defensins, yet does not provide any connection between the cysteine residues and the antimicrobial activity and mode of action of the defensins. Thus, there is no express teaching in Bulet that cysteines are responsible, in whole or even in part, for the antimicrobial properties of these compounds.

Bulet similarly does not imply a nexus between cysteine and antimicrobial activity. The cysteines are described only as participating in the secondary structure (disulfide bonds, beta-sheets, and mixed alpha-helical/beta-sheet structures) (see, Abstract). This agrees with the known structural role cysteine residues play in proteins generally. Thus, any inference that cysteines are responsible for the antimicrobial properties of defensins is mere unsupported speculation going beyond even the authors' understanding.

Applicants further submit that the presence of cysteine in a protein is not an appropriate ground to reject the claims. Paradoxically, the Rejection agrees that "Bulet et al. … do not teach 'the use of cysteine as a preservative,'" yet suggests that it is sufficient that defensins contain cysteine (see, February 4, 2008 Office Action , page 3, lines 16-17). The claimed compositions utilize cysteine in free form (*i.e.*, not connected to other amino acids via a peptide bond). This is illustrated by the description of cysteine in the specification (see, Specification page 4, lines 28-29, and page 17, Example 1). The presence of cysteine in a protein, even an antimicrobial protein, is not a teaching or suggestion to use cysteine, or that cysteine provides the antimicrobial property. Thus, Bulet demonstrably fails to describe or suggest the cysteine element of the claims, and its combination with the other references fails to describe or suggest the combination of cysteine with propofol as claimed.

To summarize, Mirejovsky and Mishra, alone or in combination do not teach or suggest compositions comprising propofol and cysteine. Bulet does not remedy the deficiencies of Mirejovsky and Mishra. As acknowledged in the Rejection itself, and as illustrated by the foregoing discussion, Bulet does not teach or suggest that

cysteine is antimicrobial, does not teach or suggest to isolate or use free cysteine for antimicrobial purposes, and does not teach or suggest compositions comprising propofol and cysteine. Accordingly, all of the limitations of the claimed invention are not taught by the cited art, whether considered individually or in the combination suggested by the rejection. Lacking the first element of a *prima facie* case for obviousness, the rejection of the claims as obvious in view of Mirejovsky, Mishra, and Bulet is thus improper.

B. The cited references and knowledge generally available in the art do not provide a motivation to combine or modify the references to arrive at the claimed invention.

The rejection argues that one of skill would have been motivated to combine the reference disclosures because the compositions described by Mishra contain antimicrobial agents such as cysteine (see, February 4, 2008 Office Action, page 6, lines 9-12). But Mishra simply doesn't teach or suggest that free cysteine is antimicrobial, or that cysteine should be combined with propofol.

The rejection suggests that cysteine is known to be an antibacterial agent, and that Mishra's antimicrobial agent thus "may be cysteine." (see, February 4, 2008 Office Action, page 6, lines 1-2). As established above, no evidence of record teaches or suggests that cysteine is antimicrobial, and no evidence has been made of record to demonstrate that it is known in the art that cysteine is antimicrobial. Certainly Mishra does not expressly teach or suggest that its optional antimicrobial agent can be cysteine; cysteine is not mentioned anywhere in the document. Even assuming, *arguendo*, that it could be argued that the blanket statement in Mishra regarding the optional use of antimicrobial agents encompasses the use of every conceivable antimicrobial agent (and Applicants are not conceding that Mishra stands for such a proposition), those of skill in the art would not understand the scope of suitable antimicrobial agents to include cysteine. To suggest that Mishra contemplates that cysteine could be used as an antimicrobial agent in its compositions simply lacks any evidentiary basis in Mishra or elsewhere in the record. Thus, Mishra provides no express or implied teaching or suggestion to to prepare a composition comprising propofol and cysteine as claimed.

Indeed, such a suggestion runs counter to the thrust of Mishra's invention. The benefit Mishra assigns to its compositions is that they do "not require the addition of any antimicrobial preservative agents." (see, Col. 4, lines 33-36). Although Mishra suggests that their compositions can optionally contain antimicrobial agents (see, Col. 5, lines 46-51), the reference on the whole emphasizes compositions "devoid of additional bactericidal or bacteriostatic preservative agents." (see, claims 37 and 38).

One of skill would not have been motivated to modify the teachings of Mishra based on the teachings of Bulet. Bulet does not teach or suggest that cysteine is antimicrobial. At most, Bulet describes antimicrobial proteins that contain cysteine residues. As set forth above, Bulet does not provide so much as a suggestion that cysteine is wholly or partially responsible for the antimicrobial properties of insect defensins. Without a nexus between cysteine and antimicrobial activity, one of skill in the art would have no reason to isolate cysteine residues from the defensin proteins described by Bulet, or otherwise even try to use purified cysteine as an antimicrobial agent. This is further supported by the fact that many proteins known in the art contain cysteine residues and cysteine domains, yet have no antimicrobial activity whatsoever. Bulet provides no express or implied teaching or suggestion to include cysteine in the propofol compositions described by Mishra or Mirejovsky.

The cited art provides no express or implied suggestion to modify their respective teachings to arrive at the claimed invention. Moreover, the lack of knowledge in the art regarding cysteine's antimicrobial potential, particularly as concerns its capacity to serve as a preservative for pharmaceuticals, compels a conclusion that no motivation to combine or modify the cited art to prepare propofol compositions comprising cysteine has been established.

C. One of skill in the art would not have a reasonable expectation of success upon combining the cited art to arrive at a composition comprising propofol and cysteine.

The rejection has not articulated any rationale to indicate why one of skill in the art would have a reasonable expectation of success in using cysteine as a preservative for propofol formulations when considering the cited art. MPEP §2143.02. Nevertheless, successful use of cysteine as a propofol preservative would not have been predictable on the basis of the teachings of the cited references, or of the knowledge available in the art.

None of the cited references, when considered individually or in combination teach or suggest that cysteine is antimicrobial, and no evidence has been provided to demonstrate that it was known in the art that cysteine is antimicrobial. Even taking the extraordinary leap of inferring that cysteine plays a role in the antimicrobial properties of insect defensins would not lead one of skill in the art to predict that cysteine in isolated form, as distinct from its intermolecular interactions with other amino acids within the three-dimensional structure of insect defensins, would exhibit antimicrobial activity generally. By extension, there is no basis from which to predict that cysteine could serve as an effective preservative for pharmaceutical compounds such as propofol.

The cited art provides no factual underpinnings from which one of skill in the art could have reasonably predicted that cysteine would have antimicrobial activity, and the available knowledge in the art does not remedy the deficiencies of the references. Accordingly, those of skill in the art would not have a reasonable expectation that the claimed invention would function successfully from the individual or combined consideration of Mirejovsky, Mishra, and Bulet.

D. A *prima facie* case for obviousness has not been established and the rejection should be reversed.

The rejection has not established any of the three elements underlying a *prima facie* case for unpatentability on obviousness grounds. The foregoing discussion demonstrates that the cited art, whether considered alone or in any combination, do not teach all of the limitations of the claimed invention, do not provide a motivation to combine or modify their respective teachings, and do not provide an expectation of success in arriving at the claimed invention. The

rejection of claims 1-8 and 10-16 under 35 U.S.C. §103(a) is improper and should be reversed.

VIII. CLAIMS APPENDIX

1. (Original) A pharmaceutical composition comprising propofol and cysteine.

2. (Original) The pharmaceutical composition of claim 1, further comprising one or more excipients.

3. (Original) The pharmaceutical composition of claim 1, further comprising a GRAS excipient.

4. (Original) The pharmaceutical composition of claim 1, further comprising purified poloxamer, Ammonium acetate, Benzalkonium chloride, Benzethonium chloride, Benzyl alcohol, Brij 35, Brij 97, Calcium gluceptate, ChlorobutanOL, Citric Acid, Cremophor EL, Deoxycholate, Diethanolamine, Ethanol, Gamma cyclodextrin, Glycerin, Lactobionic acid, Lysine, Magnesium chloride, Methylparaben, PEG 1000, PEG 300, PEG 3350, PEG 400, PEG 600, Poloxamer 188, Poloxamer 237, Poloxamer 338, Poloxmer 407, Polyoxyethylene 100 stearate, Polyoxyethylene 40 stearate, Polyoxyethylene 50 stearate, Polysorbate 20, Polysorbate 80, Povidone, Propylene Glycol, Sodium acetate, Vitamin E TPGS, Sodium benzoate, Sodium tartate, vegetable oil, soy bean oil, safflower oil, cottonseed oil, corn oil, sunflower oil, arachis oil, castor oil, olive oil, an ester of a medium or long-chain fatty acid, a palmitate, a glyceral ester, polyoxyl hydrogenated castor oil, ethoxylated ethers, polypropylene-polyethylene block co-polymers, phosphatides, egg phosphatide, soy phosphatide, glycerin, ascorbic acid, gentisic acid, or monosodium glutamate.

5. (Original) The pharmaceutical composition of claim 1, wherein said composition is: a. an aqueous solution; or b. a non-aqueous solution.

6. (Original) The pharmaceutical composition of claim 1, wherein said cysteine is of sufficient concentration to allow a no more than 10-fold increase in growth of each of Staphylococcus aureus ATCC 6538, Escherichia coli ATCC 8739, Pseudomonas aeruginosa ATCC 9027 and Candida albicans ATCC 10231 for at least 24 hours as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said composition at approximately 50 colony forming units per ml, at a temperature in the range 20.degree. C. to 25.degree. C., whereafter said aliquots are incubated at 20.degree. C. to 25.degree. C. for 24 hours and thereafter tested for viable counts of said organism.

7. (Original) The pharmaceutical composition of claim 1, wherein said composition is administered: a. intraveneous; b. intramuscular; or c. intrathecal.

8. (Original) The pharmaceutical composition of claim 1, wherein the pH of said composition is: a. between about 4.5 and about 9; b. between about 5 and about 7; c. between about 5 and about 6; or d. between about 5.5 and about 6.

9. (Withdrawn) A method of treating a patient by administering the pharmaceutical composition of claim 1.

10. (Original) The pharmaceutical composition of claim 1, further comprising a local anesthetic.

11. (Original) A pharmaceutical composition, comprising: (a) propofol; (b) a water immiscible solvent; (c) a surfactant; and (d) cysteine or a salt thereof.

12. (Original) The pharmaceutical composition of claim 11, further comprising: a. a tonicity modifier; b. glycerol; or c. a pH modifier.

13. (Original) The pharmaceutical composition of claim 11, wherein said propofol is at a concentration of: a. about 0.5 to 2.5% w/v; b. about 0.5 to 1.5% w/v; c. about 0.9 to 0.1% w/v; or d. about 1% w/v.

14. (Original) The pharmaceutical composition of claim 11, wherein said water immiscible solvent is: a. selected from the group consisting of: i) soybean oil; ii) vegetable oil; and iii) a medium or long-chain fatty acid; and b. present at a concentration of: i) from about 5 to about 15% w/v; i) from about 8 to about 12% w/v; i) from about 9 to about 11% w/v; or i) about 10% w/v.

15. (Original) The pharmaceutical composition of claim 11, wherein said surfactant is: a. selected from the group consisting of: i) polypropylene-polyethyle- ne block co-polymers; ii) egg phosphatide; and iii) soy phosphatide; and b. present at a concentration of: i) from about 0.5 to about 5% w/v; ii) from about 0.5 to about 2% w/v; iii) from about 1 to about 1.5% w/v; or iv) about 1.2% w/v.

16. (Original) The pharmaceutical composition of claim 11, wherein said cysteine is: a. cysteine; or a salt thereof; and b. present at a concentration of: i) from about 0.5 to about 5% w/v; ii) from about 0.5 to about 2% w/v; iii) from about 0.9 to about 1.5% w/v; or iv) about 1% w/v.

17. (Cancelled)

IX. EVIDENCE APPENDIX

No evidence aside from the cited art has been made of record by either Applicants or the Examiner.

X. RELATED PROCEEDINGS APPENDIX

There are no related appeals or interferences related to the subject matter of this Appeal. Accordingly, no decisions have been rendered by any court or by the Board concerning this application.

Respectfully submitted,

/Brian A. Cocca/

Paul F. Prestia, Reg. No. 23,031
Glenn E. J. Murphy, Reg. No. 33,539
Brian A. Cocca, Ph.D., Reg. No. 58,583
Attorneys for Applicants

Dated: July 16, 2008

P.O. Box 980
Valley Forge, PA 19482-0980
(610) 407-0700

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